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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,624	01/27/2006	Alexander Ian Smith	DAVI-001/00US 040722-2001	5599

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EXAMINER	
MA, JAMESON Q	

ART UNIT	PAPER NUMBER
4153	

MAIL DATE	DELIVERY MODE
10/30/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,624	SMITH ET AL.	
	Examiner	Art Unit	
	JAMESON Q. MA	4153	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 January 2008* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20060717,20070529*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Double Patenting

1. Applicant is advised that should claim 12 be found allowable, claim 13 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 1, the phrase "optionally" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Regarding claims 12-14, the limitation "said peptides" renders the claim indefinite, because it is unclear whether said peptides refers to a "library of peptides" from (i) of claim 1, or “peptides” from (vi) of claim 1.

Regarding claim 28, the phrase “substantially as hereinbefore described with reference to the examples and/or figures” renders the claim indefinite because it is unclear what the claim is referring to.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-2, 4, 9-10, and 14-21 and 25-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Jindal et al. (US 6,358,692).

Regarding claims 1 and 28, Jindal discloses a method for the detection of bioactive peptides derived from a precursor protein or protein-containing biological extract (see C1/L45-50 and C5/L35-39), comprising the steps of:

(i) providing a library of peptides derived from said precursor protein or protein-containing biological extract (see C1/L45-50 and C5/L35-39);

(ii) optionally screening said library to confirm that it includes peptides exhibiting one or more biological activities (see C3/L19-26: ligands having the first binding characteristic will bind to the target of interest reads on confirming biological activity);

(iii) separating said library to provide fractions of the library (see C3/L27-29);

(iv) screening said fractions to identify active fractions which include peptides exhibiting said one or more biological activities (see C3/L29-33: see "screening for second dimension");

(v) optionally separating each said active fraction to provide sub-fractions thereof, and screening said sub-fractions to identify active sub-fractions which include peptides exhibiting said one or more biological activities (see C3/L29-34);

(vi) isolating from said active fractions or active sub-fractions one or more peptides exhibiting said one or more biological activities (Jindal teaches the screening of peptide libraries (see C28/L28-30), so the steps of eluting ligands having desired binding characteristics (see C3/L29-34) involves isolating peptides exhibiting one or more biological activities).

Regarding claim 27, Jindal discloses all of the claim limitations as set forth above. Additionally, Jindal discloses an isolated peptide exhibiting one or more biological activities, which has been detected by the disclosed method (see C3/L29-34).

Regarding claims 2 and 4, Jindal discloses all of the claim limitations as set forth above. Additionally, Jindal discloses the method wherein said library of peptides is derived by enzymatic cleavage or physical digestion (see C8/L1-4: enzymatic digestion reads on both enzymatic cleavage and physical digestion).

Regarding claim 9, Jindal discloses all of the claim limitations as set forth above. Additionally, Jindal discloses the method wherein said library of peptides is provided by chemical synthesis (see C1/L59-61).

Regarding claim 10, Jindal discloses all of the claim limitations as set forth above. Additionally, Jindal discloses the method wherein said peptides comprise at least 2 amino acids (Having at least 2 amino acids is an inherent property of all peptides).

Regarding claim 14, Jindal discloses all of the claim limitations as set forth above. Additionally, Jindal discloses the method wherein said peptides comprise peptides whose biological activity is not predictable by amino acid sequence analysis (see C14/L21-25 and C1/L59-61: since millions of compounds can be screened, and many of these will be peptides

that were synthesized by random combinations of amino acids, it is inherent that many of these peptides will have biological activity not predictable by amino acid sequence analysis).

Regarding claims 15-17, Jindal discloses all of the claim limitations as set forth above. Additionally, Jindal discloses the method wherein said precursor protein is:

- naturally occurring protein (see C8/L1: natural libraries).
- a non-naturally occurring protein (see C36/L6: a recombinant protein is a non-naturally occurring protein).
- a recombinant protein (see C36/L6).

Regarding claims 18-21, Jindal discloses all of the claim limitations as set forth above. Additionally, Jindal discloses the method wherein said biological activity:

- is agonist activity (see C16/L52).
- is antagonist activity (see C16/L52).
- relates to any human condition (see C6/L52: immune agonist/antagonist activity is inherently related to a human condition).
- relates to conditions selected from the group consisting of arterial and venous thrombosis, inflammation, angiogenesis and cancer (agonist activity is related to cancer, as evidenced by Spicer et al. (Future possibilities in the prevention of breast cancer Luteinizing hormone-releasing hormone agonists): see abstract).

Regarding claims 25-26, Jindal discloses all of the claim limitations as set forth above. Additionally, Jindal discloses the method wherein said fractionation step (iii) and/or step (v) is carried out by:

- a fractionation method selected from the group consisting of chromatography, field flow fractionation and electrophoresis (see C3/L27-29: size exclusion is a form of column chromatography).
- chromatography (see C3/L27-29: size exclusion is a form of column chromatography).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jindal et al. (US 6,358,692) as applied to claim 9 above.

Regarding claim 11, Jindal discloses all of the claim limitations as set forth above, but the reference does not explicitly disclose the method wherein said peptides comprise at least 5 amino acids. As the number and complexity of randomized bioactive molecules available for screening of lead compounds for pharmaceutical applications and drug discovery would increase with additional amino acids added to the peptide chain, the precise number of amino acids in the synthesized peptides would have been considered a result effective variable by one having ordinary skill in the art at the time the invention was made. As such, without showing unexpected results, the claimed number of amino acids cannot be considered critical. Accordingly, one of ordinary skill in the art at the time the invention was made would have optimized, by routine experimentation, the number of amino acids in the peptides in the method of Jindal to obtain the desired number and complexity of peptides when screening for lead compounds in pharmaceutical applications and drug discovery (In re Boesch, 617 F.2d. 272, 205 USPQ 215 (CCPA 1980)), since it has been held that where the general conditions of the claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. (In re Aller, 105 USPQ 223).

10. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jindal et al. (US 6,358,692) as applied to claim 1 above, in view of Smith (Chemical Cleavage of Polypeptides).

Regarding claim 3, Jindal discloses all of the claim limitations as set forth above. However, Jindal does not explicitly disclose the method wherein said library of peptides is derived by chemical cleavage of the precursor protein or protein-containing biological extract.

Smith teaches that chemical methods may be used to cleave proteins and peptides like endoproteolytic enzymes (see P57/L1-3).

Jindal and Smith are analogous because both references are directed to peptide cleavage.

It would have been obvious to one of ordinary skill at the time of invention to substitute for the step of enzyme cleavage of Jindal, chemical cleavage as taught by Smith, because doing so would have amounted to nothing more than the simple substitution of one known peptide cleavage method for another to obtain predictable results.

11. Claims 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jindal et al. (US 6,358,692) as applied to claim 1 above, in view of Herman et al. (Optimization of the synthesis of peptide combinatorial libraries using a one pot method).

Regarding claims 5-7, Jindal teaches the use of libraries to screen for possible drug compounds (see C7/L57-62). Jindal also teaches the synthesis of a soluble peptide combinatorial library or SPCL (see C29/L23-24).

Jindal does not explicitly disclose the method wherein:

- said precursor protein or protein-containing biological extract, or said unfractionated peptide library is subjected to a determination of optimal cleavage conditions by monitoring the extent or progress of cleavage or digestion.
- said determination comprises mass spectometry analysis.
- said determination comprises MALDI-ToF MS analysis.

Herman teaches the use of combinatorial libraries to serve as a source of potential candidates in drug discovery (see P147/C1/L1-4). Herman also discloses that following the synthesis of SPCLs, MALDI-ToF mass spectrometry was used to judge the overall quality of the formed peptide libraries (see P148/C2/L5-15). Herman further discloses that the quality of a combinatorial peptide library is dependent upon the cleavage cocktail (see P149/C2/L29-33). Herman further teaches that samples cleaved with different reagents provided libraries with different amino acid balances (see P152/C1/L19-24).

Jindal and Herman are analogous because both references are directed to the synthesis of SPCLs for the purpose of drug discovery.

It would have been obvious to one of ordinary skill at the time of invention to optimize the SPCL synthesis method of Jindal, by MALDI-ToF analysis in order to optimize cleavage conditions as taught by Herman, in order to obtain a desired amino acid balance in the synthesized peptide library.

12. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jindal et al. (US 6,358,692) in view of Herman et al. (Optimization of the synthesis of peptide combinatorial libraries using a one pot method) as applied to claims 5-7 above, and further in view of Papac et al. (Mass spectrometry innovations in drug discovery and development).

Regarding claim 8, modified Jindal discloses all of the claim limitations as set forth above.

Further Herman teaches the use of MALDI-ToF in determining optimal cleavage conditions (see Herman P147/C1/L1-4, P148/C2/L5-15, P149/C2/L29-33, and P152/C1/L19-24). Modified Jindal does not explicitly disclose the method wherein said determination is automated.

Papac teaches that MALDI-ToF is capable of being automated for unattended protein identification for the purpose of minimizing operator involvement (see P138/C2/L1-3).

Modified Jindal and Papac are analogous because both references are directed to the use of MALDI-ToF for protein analysis.

It would have been obvious to one of ordinary skill at the time of invention to modify the method of using MALDI-ToF of modified Jindal, to incorporate automation as taught by Papac in order to reduce operator involvement.

13. Claims 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jindal et al. (US 6,358,692), as applied to claim 1 above, in view of Corthesy-Theulaz (US 6,060,241).

Regarding claims 12 and 13, Jindal discloses all of the claim limitations as set forth above. However, Jindal does not disclose the method wherein said peptides are peptide variants.

Corthesy-Theulaz teaches using conservative amino acid substitutions (read as creating peptide variants) to confer or modify physicochemical or functional properties of the proteins for the purpose of drug discovery (see C18/L7-12 and C18/L42-45).

Jindal and Corthesy-Theulaz are analogous because both references are directed to drug discovery.

It would have been obvious to one of ordinary skill at the time of invention to modify the peptides and proteins in the libraries of Jindal, with conservative amino acid substitutions as taught by Corthesy-Theulaz, in order to increase the number of potential drug compounds available to be screened.

14. Claims 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jindal et al. (US 6,358,692), as applied to claim 1 above, in view of Cree et al. (Measurement of cytotoxicity by ATP-based luminescence assay in primary cell cultures and cell lines).

Regarding claims 22-24, Jindal discloses all of the claim limitations as set forth above. Jindal teaches that compounds are screened for desired bioactivity by combining a solution of ligands to a target of interest to obtain information about binding characteristics (see C3/L17-25).

However, Jindal does not explicitly disclose the method:

- wherein said screening of step (ii) and/or step (iv) is carried out using an assay selected from the group consisting of biochemical-based assays and cell-based assays.
- wherein said assay is selected from the group consisting of luminescence based assays for platelet activation, laser-based methods for Prothrombin Time and Activated Partial Thromboplastin Time, luminescence and fluorescence based detection of cell proliferation, cell toxicity and apoptosis and in vivo assays.
- wherein said assay is high throughput and automated.

Cree teaches a method of in vitro cell toxicity assay using the luciferin/luciferase reaction (see Abstract: luciferin/luciferase reaction is a luminescence method). Cree further teaches that toxicity is tested for the purpose of drug discovery and the assays can test four drugs/agents in triplicate (see Abstract and P553/C1/L19-P553/C2/L4). Cree further teaches that the assays are conducted on 96-well microplates with 1000 cells/well for cell lines and 10000 cells/well for primary tumor tissue (see abstract: reads on high-throughput assay). Cree also teaches that the luminescence measurements are performed in a microplate luminometer (see P554/C2/L15-20: part of the assay performed in the luminometer is inherently automated).

Jindal and Cree are analogous because both references are directed to screening compounds for drug discovery.

It would have been obvious to one of ordinary skill at the time of invention to substitute for the target/ligand screening method of Jindal, the cytotoxicity screening method of Cree, because doing so would amount to nothing more than simple substitution of known methods for determining specific bioactivity in potential drug compounds, to accomplish expected results.

Conclusion

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMESON Q. MA whose telephone number is (571)270-7063. The examiner can normally be reached on M-R 7:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Basia Ridley can be reached on (571)272-1453. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

JM
October 23, 2008

/Basia Ridley/
Supervisory Patent Examiner, Art Unit 4153